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A SIMPLE DIASTEREOSELECTIVE SYNTHESIS OF (±)-ELDANOLIDE

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Abstract: Acid catalyzed rearrangement of 4,5-dihydro-1,3-dioxepins is a suitable method for the synthesis of 2,3-substituted tetrahydrofurans and 3,4-substituted 4-butanolides. As an example for this method, we present a large scale, diastereoselective synthesis of (±)-eldanolide, the wing gland pheromone of the male African sugar cane borer *Eldana saccharina* (Wlk.).

Eldanolide (7), the wing gland pheromone of the male African sugar cane borer Eldana saccharina (Wlk.), was first isolated in 1981 by Kunesch et al.$^{1)}$. By synthesizing both enantiomers of 7 and comparison of their CD spectra with those of the natural pheromone, Vigneron et al. and Larchevêque et al.$^{2,3)}$ were the first to show the absolute configuration of natural 7 to be the 3S,4R-configuration. Since then some other diastereo- and enatioselective syntheses have been published$^{4-6)}$.

Recently, we described a new diastereoselective route to 2,3-substituted tetrahydrofurans and 3,4-substituted 4-butanolides starting with 4,7-dihydro-1,3-dioxepins$^{7)}$. This method was applied to the synthesis of (±)-7. So we now wish to report a simple diastereoselective, large scale synthesis of (±)-7.

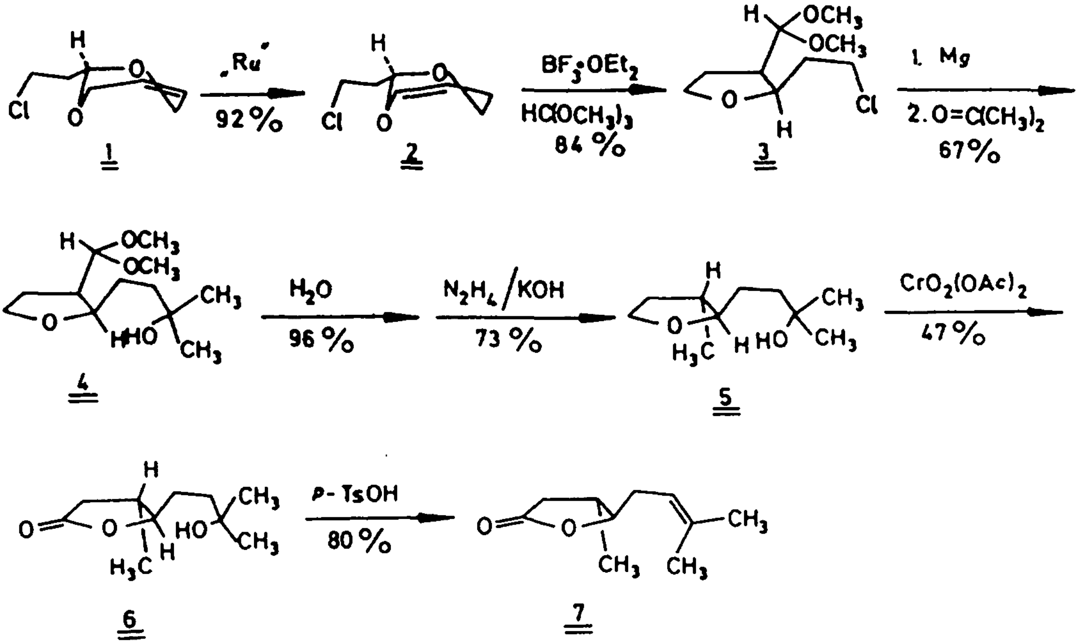
2-(2'-Chloroethyl)-4,7-dihydro-1,3-dioxepin (1), easily available from 3-chloro-1,1-dimethoxypropane and cis-2-butene-1,4-diol by acid catalyzed alcohol exchange, is readily transformed to the corresponding 4,5-dihydro-1,3-dioxepin 2 by isomerization with 0.15 mol% "activated" $RuCl_2(PPh_3)_3$ as catalyst$^{8)}$. The activation is simply carried out by treatment of a methanolic solution of $RuCl_2(PPh_3)_3$ with $NaBH_4$.

Key step in the reaction sequence is the acid catalyzed ring contraction of 2 to the appropriate tetrahydrofuran-3-carboxaldehydes, which is carried out in CH_2Cl_2 with $BF_3 \cdot Et_2O$ as catalyst at -30°C. The aldehydes are trapped with trimethylorthoformiate as the corresponding acetals 3 in a cis/trans ratio of 70:30.

The desired carbon skeleton for the synthesis of 7 is obtained by a Grignard reaction of the cis/trans-mixture of 3 with acetone to give 4. After deprotecting with diluted hydrochloric acid, the aldehyde function in the 3-position of 4 is reduced by the Wolff-Kishner procedure with N_2H_4/KOH to the methyl group[9]. Due to the strong basic conditions of this procedure, epimerization in the 3-position of 5 is observed yielding predominantly the desired trans-5 (trans/cis-ratio = 90:10).

The tetrahydrofuran derivative 5 is transformed to lactone 6 by oxidation with CrO_3/Ac_2O in benzene. Since trans-5 shows more selectivity in the oxidation step, the trans/cis ratio of 6 is improved to 96:4. Dehydration of 6 is performed with p-toluenesulfonic acid in benzene by azeotropic removal of water following the procedure already described by Chandrasekaran et al.[6].

The structure of (±)-7 is assigned by its comparison of spectroscopic and physical values with literature data.



EXPERIMENTAL

^1H NMR spectra were obtained on a Varian EM 390, ^{13}C NMR spectra on a Varian CFT 20 in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin Elmer 377 as liquid films. Gaschromatography was performed on a Carlo Erba, mod. Fractovap 2101, electrometer mod. 180, column 3 m 5% Apiezon L on Gaschrom 80-100 mesh. Solutions were dried over anhydrous magnesium sulfate and solvents by standard methods.

2-(2'-Chloroethyl)-4,7-dihydro-1,3-dioxepin (1)

276 g (2 mol) 3-Chloro-1,1-dimethoxypropane, 176 g (2 mol) cis-2-butene-1,4-diol and 1 g p-toluenesulfonic acid in 1200 ml cyclohexane are boiled under reflux with stirring. Methanol is distilled off over a packed column with cyclohexane as azeotrope (bp=54,2°C, 37% methanol). When the temperature has reached the boiling point of the pure cyclohexane (bp=81,4°C), the reaction mixture is neutralized with 100 ml of 2 m NaOH. After drying and removal of cyclohexane, the product is distilled under reduced pressure.

Yield: 309 g (1.90 mol, 95%), colourless liquid, bp=86-89°C/10mm Hg.- IR: 3020 (CH olef.), 2935, 2880, 2840 cm^{-1}(CH).- ^{1}H NMR: δ = 5.7-5.5 (m, 2H, olef.-H), 4.88 (t, J=6.0Hz, 1H, O-CH-O), 4.50-3.90 (m,4H,O-CH$_2$-C=C), 3.56 (t, J=6.8Hz, 2H, CH$_2$Cl), 2.04 ppm (q, 2H, C-CH$_2$-C).- $C_7H_{11}ClO_2$ (162.6) calc. C, 57.70; H, 6.82, found C, 57.59; H, 6.79%.

2-(2'-Chloroethyl)-4,5-dihydro-1,3-dioxepin (2)

325 g (2 mol) 1 in 300 ml ethanol are degassed with nitrogen. Then, 3.8 g (0.004 mol; 0.15 mol%) RuCl$_2$(PPh$_3$)$_3$ and 4 g NaBH$_4$ are added. After addition of NaBH$_4$, the brown colour turns off within a few minutes to orange-yellow, and the reaction mixture comes to boiling. When the exothermic reaction has finished, the solvent is removed, and the residue is distilled unter reduced pressure. Yield: 299 g (1.84 mol, 92 %), colourless liquid, bp= 77-79°C/10 mmHg.- IR: 3035 (CH olef.), 2960, 2920, 2870 (CH), 1645 cm^{-1} (C=C).- ^{1}H NMR (CDCl$_3$): δ = 6.30 (dd, J=7.5 und 3Hz, 1H, C=CH-O), 4.83 (dt, 7.5 and 3 Hz, 1H, CH=C-O), 4.61 (t, J=4.8 Hz, 1H, O-CH-O), 4.08 (ddd, J=11.4, 5.6 and 2.5 Hz, 1H, O-CH$_2$), 3.62 (t, J=6.8 Hz, 2H, CH$_2$Cl), 3.25 (td, J=11.4 and 2.7 Hz, 1H, O-CH$_2$), 2.70-1.90 (m, 2H, CH$_2$-C=C), 2.14 ppm (q, 2H, C-CH$_2$-C).- $C_7H_{11}ClO_2$ (162.6) calc. C, 57.70; H, 6.82, found C, 57.76; H, 6.78%.

2-(2'-Chloroethyl)-3-dimethoxymethyl-tetrahydrofuran (3)

244 g (1.5 mol) 2 in 600 ml methylene chloride are cooled to -70°C. Then 40 ml BF$_3$. OEt$_2$ and 167 g trimethylorthoformiate (1.575 mol, 105% of the theoretical amount) are added. While stirring, the temperature is allowed to rise up with 3-4°C per hour. At -10°C, 150 ml 10 m NaOH are added with vigorous stirring and cooling with dry ice/acetone. Then 200 ml of water are added. After separation of the layers, the organic layer is washed with water and dried. After removal of the solvent, the residue is distilled unter reduced pressure. Yield: 263 g (1,26 mol, 84%), cis/trans= 70/30, colourless oil, bp= 55-60°C/0.1 mmHg.- IR: 2940, 2880, 2830 (CH), 1720 cm^{-1}. ^{1}H NMR: δ = 4.26 (d, J=9Hz, 1H, CH(OCH$_3$)$_2$, 4.15-3.50 (m, 3H, CH$_2$-O-CH), 3.62 (t, J= 6.8Hz, 2H,CH$_2$Cl), 3.32 (s, 3H, OCH$_3$), 3.30 (s, 3H, OCH$_3$), 2.80-2.35 (m, 1H, CH-CH (OCH$_3$)$_2$), 2.20-1.70 ppm (m, 4H, C-CH$_2$-C).- $C_9H_{17}ClO_3$ (208.7) calc. C, 51.80; H, 8.21, found C, 51.76; H, 8.23%.

2-(3'-Hydroxy-3'-methylbutyl)-3-dimethoxymethyl-tetrahydrofuran (4)

24.3 g (1 mol) Mg-turnings in 50 ml ether are activated with 1-2 ml 2-bromopropane. When the reaction has started, 208.7 g (1 mol) 3 in a mixture of 350 ml ether and 100 ml THF are added at such a rate, that the reaction mixture boils under reflux. After complete addition, the mixture is boiled for 1 1/2 h under reflux. Then, 58 g (1 mol) acetone in 200 ml THF is added, and boiling is continued for 2 h followed by hydrolysis with a solution of 100 g NH$_4$Cl and 110 ml conc. HCl in 400 ml water. After separation of the two layers, the aqueous layer is extracted twice with 150 ml ether. The combined organic layers are dried. After removal of solvent, the product is distilled under reduced pressure. Yield: 155 g (0.67 mol, 67%), cis/trans= 70/30, colourless oil, bp= 80-85°C/0.1 mmHg.- IR: 3440 (OH), 2960, 2820 (CH), 1140, 1110 (C-O-C), 1065 cm^{-1} (C-OH).- ^{1}H NMR: δ = 4.35 (d, J=8.4Hz, 1H, CH (OCH$_3$)$_2$), 4.00-3.60 (m, 3H, CHO-C), 3.32 (s, 6H, OCH$_3$), 3.15 (s, 1H, OH), 2.65-2.35 (m, 1H, CH-CH (OCH$_3$)$_2$), 2.20-1.40 (m, 6H, C-CH$_2$-C), 1.20 ppm (s, 6H, CH$_3$). $C_{12}H_{24}O_4$ (232.3) calc. C, 62.05; H, 10.41, found C, 62.13; H, 10.38%.

2-(3'-Hydroxy-3'-methylbutyl)-3-methyl-tetrahydrofuran (5)

232 g (1 mol) 4 are hydrolyzed by stirring for 6 h at room temperature with a mixture of 200 ml THF, 300 ml H$_2$O and 50 ml conc. HCl. After neutralization with Na$_2$CO$_3$, the organic layer separated. The aqueous layer is extracted with 200 ml ether. The organic layers are combined, and after removal of solvent, the residue is added to a mixture of 100 ml N$_2$H$_4$·H$_2$O, 600 ml diethyleneglycol and 100 g KOH. The temperature is rised to 120°C, then slowly to 200°C and kept at this temperature, until no more nitrogen is evolved. After cooling, the reaction mixture is poored into 1,5 l of water, and extracted four times with 200 ml ether. After drying and removal of solvent, the residue is distilled under reduced pressure. Yield: 120.6 g (0.7 mol, 70%), cis/trans= 10:90, colourless oil, bp= 40-45°C/0.04 mmHg.- IR: 3440 (OH), 2960, 2870 (CH).- ^{1}H NMR: δ =3.90-3.60 (m, 3H, CH$_2$-O-CH), 3.30 (s, 1H,OH), 2.30-1.30 (m, 7H, C-CH$_2$-C, CH-CH$_3$), 1.18 (s, 6H, C(OH)-CH$_3$)$_2$), 1.02 ppm (d, J=6.3Hz, 3H, CH-CH$_3$).- $C_{10}H_{20}O_2$ (172.3) calc. C, 69.71; H, 11.70, found C, 69.58; H, 11.68%.

5-(3'-Hydroxy-3'-methylbutyl)-4-methyldihydrofuran-2-one (6)

To 86 g (0.5 mol) 5 in 500 ml benzene is added dropwise a solution of 66.5 g CrO$_3$ in 250 ml acetic anhydride between 0 and 5°C. After complete addition, the solution is stirred for 12 h at ambient temperature . Then, a solution of 67 g NaOH in 500 ml water is added at such a rate, that the temperature is maintained below 40°C. After separation of the organic layer, the aqueous layer is extracted with 500 ml ether. To the combined organic layers is added a saturated Na$_2$CO$_3$-solution. After drying and removal of the solvent, the residue is distilled under reduced pressure.- Yield: 43.7 g (0.235 mol, 47%) cis/trans= 4:96, colourless oil, bp= 145-150°C/0.1

mmHg.- IR: 3440 (OH), 2965, 2930, 2875 (CH), 1770 cm^{-1} (C=O).- ^{1}H NMR: δ =4.15-3.90 (m, 1H, CH-O-C), 3.30 (s, 1H, OH), 2.90-2.45 (m, 2H, O=CO-CH$_2$), 2.45-1.40 (m, 5H, C-CH$_2$-C, C-CH-C), 1.23 (s, 6H, C(OH)(CH$_3$)$_2$), 1.15 ppm (d, J=6.3Hz, 3H, CH-CH$_3$).- ^{13}C NMR: δ =176.74 (COO), 87.87 (CH-OOC), 69.93 (COH), 39.41 (CH$_2$-COH), 37.01 (CH-COO), 35.96 (CH-CH$_3$), 29.38 and 28.93 (COH(CH$_3$)$_2$), 28.69 (CH$_2$-CH$_2$-COH), 17.37 ppm (CH$_3$-CH). $C_{10}H_{18}O_3$ (186.3) calc. C, 64.47; H, 9.74, found C, 64.61; H, 9.88%.

4-Methyl-5(3'-methyl-2'-butenyl)-dihydrofuran-2-one (7) (±) Eldanolide)

37.2 g (0,2 mol) 6 and 3 g p-toluenesulfonic acid in 300 ml benzene are boiled to reflux. Over a packed column, the water is azeotropically removed with benzene. Then the reaction mixture is washed with aqueous NaOH and water. After drying and removal of the solvent, the residue is distilled under reduced pressure. Yield: 26,8 g (0.16 mol, 80%) cis/trans = 4:96, colourless liquid, bp 71-74°C/0.1 mmHg.- IR: 2965, 2930, 2875 (CH), 1785 cm^{-1} (C=O).- ^{1}H NMR: δ = 5.15 (t, 1H, CH=C), 4.04 (q, J=6Hz, 1H, CH-O), 2.80-2.00 (m, 5H, CH$_2$-C=C, OOC-CH$_2$-CH) 1.71 and 1.63 (2s, 6H, C=C(CH$_3$)$_2$); 1.12 ppm (d, J=6.3Hz, 3H, CH-CH$_3$).- ^{13}C NMR: δ = 176.44 (COO), 135.27 (=C(CH$_3$)$_2$), 118.04 (CH=), 87.06 (CH-OOC), 37.00 (CH-COO), 35.10 (CH-CH$_3$) 32.18 (CH$_2$-COH), 25.79 and 17.93 (=C(CH$_3$)$_2$ E and Z) 17.66 ppm (CH$_3$-CH). $C_{10}H_{16}O_2$ (168.2) calc. C, 71.40; H, 9.59, found C, 71.30; H, 9.46%.

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